ASSESSMENT OF CEREBRAL VASCULAR RESISTANCE IN CIRRHOTIC PATIENTS WITH HEPATIC ENCEPHALOPATHY USING TRANSCRANIAL COLOR DOPPLER ULTRASONOGRAPHY

Dissertation submitted in partial fulfillment of the requirements for the degree of

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DECLARATION

I solemnly declare that this dissertation "**Assessment of cerebral vascular resistance in cirrhotic patients with hepatic encephalopathy using transcranial color Doppler ultrasonography"** was prepared by me in the Department of Medical Gastroenterology, Madras Medical College and Government General Hospital , Chennai under the guidance and supervision of Professor and HOD, Department of Medical Gastroenterology, Madras Medical College and Government General Hospital , Chennai between January 2009 and December 2009.

This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the university requirements for the award of degree of DM Medical Gastroenterology.

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CERTIFICATE

This is to certify that **Dr Gokul B. J.** has been a post graduate student during the period July 2007 to Aug 2010 at Department of Medical Gastroenterology, Madras Medical College and Government General Hospital, Chennai.

The dissertation titled '**Assessment of cerebral vascular resistance in cirrhotic patients with hepatic encephalopathy using transcranial color Doppler ultrasonography'** is a bonafide work done by him during the study period and is being submitted to the Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the university requirements for the award of degree of DM Medical Gastroenterology.

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INTRODUCTION

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Patients with liver cirrhosis have hyperdynamic circulation, characterized by increased cardiac output, decreased peripheral vascular resistance and arterial hypotension. Transcranial Doppler (TCD) allows observation of the velocity waveform in the major cerebral blood vessels.[1] Some studies with TCD have shown that the mean cerebral blood velocity, an indicator of cerebral blood flow, is decreased or unchanged in patients with chronic liver disease. Dillon *et al* [2] reported that the mean cerebral blood velocity is decreased in advanced cirrhotic patients without encephalopathy. Lagi *et al* [3] showed no difference in the mean cerebral blood velocity between cirrhotic patients with ascites and healthy controls. Guevera *et al* [4] measured the cerebral resistive index instead of cerebral blood velocity in cirrhotics and demonstrated that the resistive index is higher in cirrhotics with ascites than in healthy controls. Pulsatility and resistive indices are widely accepted as an indicator of vascular resistance.[5] These parameters are more accurate than measurement of cerebral blood flow velocity.

Hepatic (portal-systemic) encephalopathy is a serious complication of chronic liver disease and is broadly defined as an alteration in mental status and cognitive function occurring in the presence of liver failure. Gut-derived neurotoxins that are not removed by the liver because of vascular shunting and decreased hepatic mass cause the symptoms that we know of as hepatic encephalopathy. Ammonia levels are typically elevated in patients with hepatic encephalopathy, but the correlation between severity of liver disease and height of ammonia levels is often poor. Other compounds and metabolites that may contribute to the development of encephalopathy include certain false neurotransmitters and mercaptans.

Proposed mechanisms for pathogenesis of hepatic encephalopathy

1. Accumulation of toxins (Ammonia, Mercaptans)
2. Enhanced GABAergic neurotransmission
3. Accumulation of false neurotransmitters

Evidence for reproducible alterations in soluble guanylate cyclase, nitric oxide (NO), and related pathways also has been published.[6] It is possible that alteration in cerebral blood flow could contribute to pathogenesis of encephalopathy.

This study was done to evaluate the cerebral hemodynamic parameters using TCD in cirrhotic patients with and without encephalopathy and compared then with healthy controls.

AIM OF THE STUDY

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The aim of this study is to assess the resistive and pulsatility indices which are indicators of cerebral vascular resistance in cirrhotic patients with hepatic encephalopathy using transcranial Doppler ultrasonography.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Hepatic encephalopathy (HE), or portosystemic encephalopathy, is characterised by reversible decrease in neurologic function caused by liver disease.[7] This complication can develop in about 30-45% of cirrhotics at any point of time.[8] Two major determinants for this syndrome are liver parenchymal dysfunction and portosystemic shunt. Spontaneous shunts are more prevalent inpatients with hepatic encephalopathy as compared to patients with other forms of decompensation like ascites.[9] Similarly, cognitive impairment is more common in advanced liver disease (Child C) than in Child A cirrhotics.[10] Spectrum of HE ranges from pre-symptomatic minimal HE to symptomatic over HE. Decompensation of chronic liver disease in the form of HE confers a worse prognosis. A retrospective analysis showed survival probability of 42% at one year and 23% at 3 years after presenting with an encephalopathy episode.[11]

The precise pathogenic mechanisms for HE are not fully defined. Decades of experience with animal models, including dogs with a surgically created Eck fistula (end-to-side portocaval shunt), [12] have identified the essential pathophysiologic elements. In the setting of portosystemic shunting, by which portal blood is diverted away from the liver and into the vena cava, ingestion of a protein meal is associated with the onset of encephalopathy and progression to coma and death. Although the precise mechanisms are not established, these findings suggest that absorption of nitrogenous by-products of proteins from the colon into the portal circulation plays a key role.

This pathophysiologic model of hepatic encephalopathy is simplistic in some ways and does not account for other potentially important parameters, such as changes in central neurotransmitters and the blood-brain barrier, [13] but the model fits well with clinical experience and makes no assumptions about the precise identity of the toxin(s)

involved. For example, even though creation of a portacaval shunt is highly effective for treatment of bleeding associated with portal hypertension, the clinical consequence is increased shunting and an increase in the frequency and severity of encephalopathy. [14] Therefore, recognition of these key features - portosystemic shunting and defective hepatic clearance of nitrogenous metabolites—continues to form the basis of standard treatments for HE.

Is ammonia the toxin responsible for HE? Yes, but not the only one, and the mechanisms whereby ammonia produces neuropsychiatric abnormalities are not fully defined. [15] In most relevant clinical series, elevated blood ammonia levels are detected in 60% to 80% of patients with cirrhosis and encephalopathy, and therapy aimed at decreasing the concentration of ammonia results in resolution of encephalopathy. [16] It is clear, however, that multiple metabolic abnormalities coexist, including changes in the profile of circulating amino acids, mercaptans, and central nervous system levels of dopamine and other neurotransmitters. [17] These alterations are present to a variable extent in different clinical scenarios of HE and probably work in a complementary manner to modify neurologic function in cirrhosis. Even if ammonia is not the only cause, or even the predominant cause, of HE, it is a clinically useful marker of the production of enteric toxins from nitrogenous substrates.

Detailed reviews of the pathogenesis and molecular mechanisms of HE have been published. [18] The focus on the role of ammonia and on the potential role of inhibitory neurotransmission through γ-aminobutyric acid (GABA) receptors in the central nervous system is based on the importance of ammonia as a guide to therapy and the emerging support for the GABA receptor complex as a target for newer therapies. Mechanisms involving changes in central neurotransmitters and circulating amino acids also are

relevant, but their therapeutic implications are not as well defined. It is notable, for example, that in an animal model of HE, exploratory studies using micro-array technology to detect messenger RNA (mRNA) levels have demonstrated a two-fold increase in 16 mRNA transcripts and a two-fold decrease in 15 transcripts. [23] Some of these transcripts are derived from genes involved in neurotransmitter receptors, transporters, signal transduction, and the cellular response to oxidative stress. Evidence for reproducible alterations in soluble guanylate cyclase, nitric oxide (NO), and related pathways also has been published. [20] These multiple changes and the lack of unanimity regarding which one is primary underscore the need for continued efforts to improve our understanding of this important complication of liver failure.

Ammonia hypothesis:

Ammonia is a key intermediate in nitrogen and protein metabolism, and the dynamics of ammonia handling in humans are well defined. [21] The gastrointestinal tract is the primary site of ammonia production. Nitrogenous compounds in the colon, which include ingested proteins and secreted urea, are degraded by bacteria with liberation of ammonia, which is then absorbed into the portal circulation, where concentrations are 5- to 10-fold greater than in mixed venous blood. [22] The first-pass extraction of ammonia by the liver is high, resulting in clearance of ammonia from the portal system and prevention of its entry into the systemic circulation. Within hepatocytes, ammonia is converted rapidly by a series of enzymatic reactions to nontoxic glutamine and is synthesized in separate reactions into urea for secretion by the kidneys. Abnormalities in urea cycle enzymes occur in congenital syndromes, but enzyme deficiencies are not the major concern in most patients with cirrhosis, in whom ammonia bypasses the liver as a result of portosystemic shunting.

In addition to their role in urea transport, the kidneys are a site of ammonia generation and actively secrete ammonia into the urine. Indeed, a net increase in the concentration of ammonia is observed in the renal veins as compared with the renal arteries, and the concentration of ammonia in the renal veins is increased by hypokalemia and use of diuretics. [23] Clinical studies support a role for hypokalemia in precipitating HE through an effect on renal ammoniagenesis. [28]

Following bolus injection of radiolabeled ammonia, the liver, bladder, and brain show appreciable uptake. In encephalopathy, arterial ammonia levels increase and the rate of accumulation of ammonia in the brain also increases from 32 ± 3 μmol/min to 53 ± 7 μmol/min. Because muscle is an important site of ammonia clearance, the muscle atrophy seen in advanced cirrhosis may contribute to the increase in the uptake of ammonia by the brain.

Although the implications of these observations regarding ammonia metabolism, portosystemic shunting, and the pathogenesis of HE are not fully defined, in aggregate the observations indicate a clear relationship between HE and abnormal ammonia handling.

Difficulties in the measurement and interpretation of blood ammonia levels include

(1) Substantial variations in venous as compared with arterial ammonia levels;

(2) Exercise-induced release of ammonia from skeletal muscle;

(3) A poor correlation between the absolute value of the blood ammonia level and the degree of encephalopathy; and

(4) Differences in the time course between the rise in blood ammonia levels and the onset of symptoms of encephalopathy. [29] Despite these limitations, measures to lower arterial ammonia levels remain a cornerstone of the management of hepatic coma. [30]

Patients with cirrhosis are subject to changes in systemic fluid and electrolyte balance by virtue of the sodium and water retention that accompanies cirrhosis and the frequent use of potent diuretics. Because encephalopathy commonly is precipitated by metabolic events, [32] it is instructive to consider how abnormalities in acid-base and electrolyte balance influence ammonia metabolism, with the assumption that increases in blood ammonia levels increase the severity of encephalopathy. The effects of uraemia are predictable, because urea diffuses into the colon, where it is metabolized to liberate ammonia after bacterial degradation. The effects of hypokalemia and alkalosis are more subtle. Hypokalemia frequently develops in cirrhotic patients as a consequence of diuretic-induced urinary losses, diarrhoea, vomiting, and nutritional deficiencies. First, hypokalemia increases ammonia production by the kidney. Second, hypokalemia and alkalosis favour cellular uptake of ammonia. Because most of the body's K^+ stores are found in the intracellular space, lowering K^+ concentrations in the extracellular fluid stimulates efflux of K^+ out of cells to restore extracellular concentrations. Cells compensate for the loss of K^+ by a net uptake of Na^+ and H^+ ions to maintain electroneutrality, thereby leading to relative alkalinization of the extracellular space and acidification of the intracellular space. Because ammonia (NH_3) and ammonium ion (NH_4^+) exist in equilibrium, the extracellular alkalosis increases the portion of membrane-permeable NH_3, whereas the intracellular acidosis serves to trap NH_4^+ within the cell. Therefore, the net effect of hypokalemia is a shift of ammonia into neurons or other cells, where it exerts its toxic effects. Consequently, normalizing hypokalemia is therapeutic.

Despite the strong evidence that implicates ammonia as an important contributor to HE, the precise cellular mechanisms involved remain elusive. Several potential mechanisms of ammonia-induced neuronal dysfunction have been described. Ammonia has been reported to decrease the concentration of glycogen in cultured astrocytes, [29] impair glial-neuronal communication, [30] and interfere with synaptic transmission. Over longer periods, sustained elevation of ammonia levels induces pathologic changes in perineural astrocytes. Because glycogen stores in astrocytes represent an important energy reserve for the brain, disruption of glial-neuronal signaling may play a role on the pathogenesis of HE. [31]Observations in animal models of HE and hyperammonemia support these general conclusions, although the multiple effects of ammonia and its metabolites have not been fully resolved. In addition, ammonia modulates cell signaling through effects on glutamate and GABA signaling, and alterations in ammonia metabolism and GABA signaling are thus related.

γ-Aminobutyric Acid Hypothesis:

Ammonia causes some of the symptoms and signs of HE only after it is metabolized by glutamine synthetase in the brain. In an animal model of HE, portacaval shunting has been shown to lead to increases in plasma and brain ammonia concentrations, as well as increases in brain glutamine and tryptophan levels as a result of the action of glutamine synthetase. [32] Inhibition of glutamine synthetase results in normalization of brain glutamine concentrations and normalization of glucose consumption, supporting a role for glutamine synthesis in the development of cerebral metabolic abnormalities in hyperammonemic states. Therefore, ammonia alone does not explain the central nervous system abnormalities in HE.

Studies in humans and animal models have implicated the GABA receptor complex as a key contributor to neuronal inhibition in HE.[33] (Fig 1a & 1b) The GABA receptor complex is localized to postsynaptic membranes and constitutes the principal inhibitory network in the central nervous system. The complex consists of (1) a GABA-binding site that faces the extracellular surface; (2) a Cl^--selective pore that opens in response to GABA binding to permit influx of Cl^- and produce membrane hyperpolarization; and (3) closely associated barbiturate and benzodiazepine receptor sites that potentiate the effects of GABA. The endogenous ligands for the benzodiazepine receptor have not been clearly identified.

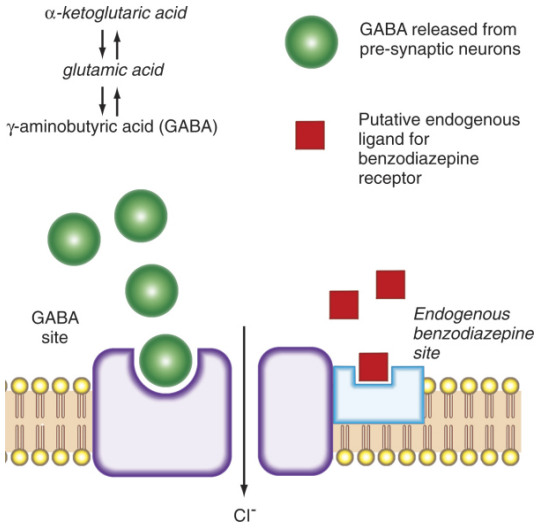


Fig 1a γ-Aminobutyric acid (GABA) receptor–chloride (Cl^-) channel complex in the postsynaptic membrane

Theoretically, increases in GABAergic transmission could result from increased availability of extracellular GABA or benzodiazepine receptor ligands. The liver contains high concentrations of GABA and GABA trans-aminase. [38] Liver injury disrupts GABA homeostatic mechanisms and may thereby contribute to the pathogenesis of HE. In addition, ammonia combines with α-ketoglutarate in the central nervous system to form

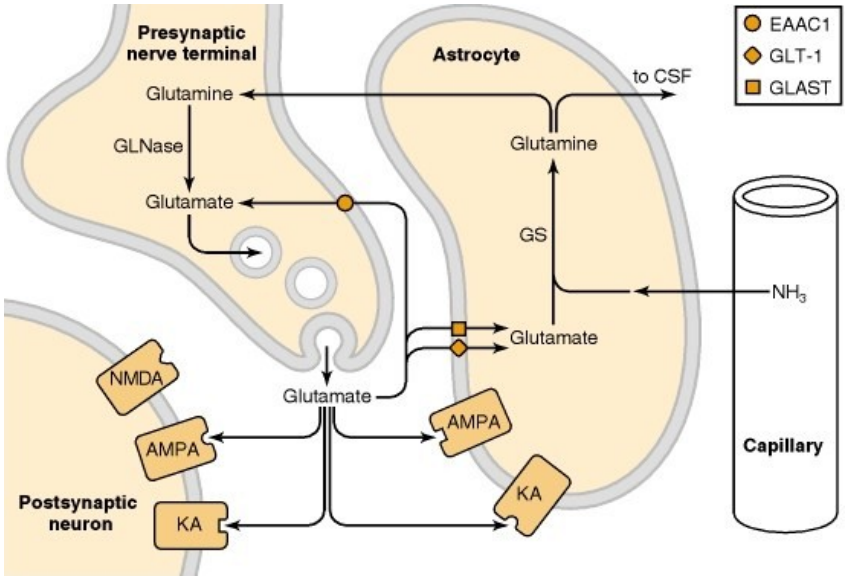


Fig 1b Major steps in glutamatergic neurotransmission. Glutamate released from the presynaptic neuron is taken up into the perineuronal astrocyte via the glutamate transporter-1 (*GLT-1*) and the glutamate—aspartate transporter (*GLAST*) or the neuronal excitatory amino acid carrier-1 (*EAAC1*). Glutamate receptors are expressed on neurons (*NMDA, AMPA*, kainate [*KA*] subtypes) and astrocytes (*AMPA, KA* subtypes). Ammonia (NH_3) removal by glutamine synthetase (*GS*) occurs only in the astrocyte. In acute liver failure, decreased expression of GLT-1 and concomitant increases of extracellular glutamate may signify impaired neuron—astrocyte trafficking. *GLNase*, glutaminase; *CSF*, cerebrospinal fluid.

glutamate, which, in turn, is amidated to produce GABA. Therefore, increased production of GABA would be expected to correlate with ammonia levels.

The evidence for the role of endogenous benzodiazepine receptor ligands in increasing GABAergic transmission, however, is stronger [35] In the absence of known ligands, putative benzodiazepine receptor agonists are identified by their competitive inhibition of flumazenil (a benzodiazepine receptor antagonist) binding. In both animal and human models, HE is associated with an increase in levels of benzodiazepine receptor ligands. Similarly, benzodiazepine-like activity is increased in cerebrospinal fluid, blood, and urine in humans with HE. Several additional points merit emphasis. First, gut bacteria provide precursors of benzodiazepine receptor ligands, just as they produce ammonia. Impairment of hepatic clearance of such ligands in patients with cirrhosis parallels the reduced clearance of ammonia, and treatment to lower ammonia levels would be expected to have similar effects on levels of benzodiazepine receptor ligands. Second, the concentration of these ligands correlates roughly with the stage of HE. Finally, HE is ameliorated in some patients by flumazenil or its structurally related analogs Ro 15-3505 and Ro 15-4513.

The efficacy of flumazenil in the treatment of HE has been studied in several clinical trials. In general, intravenous infusion of flumazenil (0.4 to 1 mg) results in modest but rapid improvement in the EEG and a more delayed improvement in the patient's mental status. [36] Some of the responders in these trials had received pharmaceutical benzodiazepines. Other studies, including blinded cross-over trials, have failed to identify a beneficial effect of flumazenil. [37] The reasons for the different results are not clear. In a literature review encompassing 13 trials and 805 patients, short-term improvement was detectable following treatment with flumazenil, but no appreciable

change in rates of recovery or mortality was observed. Therefore, most beneficial responses usually are incomplete, without full recovery to normal mental status, and are short-lived, perhaps because flumazenil-like drugs are incomplete benzodiazepine receptor blockers, or, more likely, other factors such as ammonia, mercaptans, and amino acids also contribute to HE.

These studies support a role for benzodiazepine receptor ligands in the pathogenesis of HE and suggest that flumazenil or other benzodiazepine receptor antagonists may be useful in the treatment of HE. Clearly, these agents are of benefit in reversing the effects of exogenous benzodiazepines, may provide useful prognostic information, and may aid in the differential diagnosis of coma. Although the findings in animal models are not necessarily generalizable to all forms of liver injury, the implications are intriguing: Encephalopathy may be caused in part by an increase in inhibitory neurotransmitter tone in the central nervous system. It merits emphasis that ammonia potentiates GABAergic transmission, thereby supporting the concept that the ammonia hypothesis and the GABA hypothesis are functionally related.

Nomenclature of hepatic encephalopathy:

The Working Party at the XI World Congress of Gastroenterology 1998 proposed a nomenclature that defines HE with respect to

1. The nature of hepatic abnormality
2. Duration and characteristics of neurologic manifestations. [38]

The nomenclature broadly categorises HE by the nature of hepatic abnormality into 3 types

1. Type A: HE associated with acute liver failure
2. Type B: HE associated with portosystemic bypass and no intrinsic hepatocellular disease
3. Type C: HE associated with cirrhosis and portal hypertension and/or portosystemic shunts.

TYPE A HEPATIC ENCEPHALOPATHY

It is recognised in the presence of acute liver injury which often progresses rapidly. Within hours or days, patient may deteriorate to coma. It is often associated with seizures, decerebrate rigidity and frequently, death. [39] This is associated with a high mortality rate and death is usually due to cerebral herniation and hypoxia characterised by increased intracranial pressure. Cerebral oedema is partly attributed to swelling of astrocytes. [40] The most common etiology includes acetaminophen overdose and viral hepatitis.

TYPE B HEPATIC ENCEPHALOPATHY

In type B HE, toxins bypass the liver and enter central nervous system due to the development of portosystemic shunts which connects the portal venous system supplying blood to the liver with systemic circulation. There is no associated intrinsic liver disease. Portosystemic shunts can be congenital, artificial or spontaneous. Type B HE is rare.

TYPE C HEPATIC ENCEPHALOPAHTY

It is usually associated with cirrhosis and portal hypertension with or without portosystemic shunt.

Type B and C HE are divided into categories of episodic, persistent and minimal, based on the duration and characteristics of neurological manifestations.

The Working Party recommended that the term 'subclinical' be replaced with 'minimal' because of potential misinterpretation that could arise from use of former term. It also helped to avoid medical errors induced by a name that could implicate that the condition is below the threshold of significance.

WEST HAVEN CRITERIA FOR GRADING HEPATIC ENCEPHALOPATHY [41]

GRADE 0:

1. lack of detectable changes in personality or behaviour
2. no asterixis

GRADE 1

1. Trivial lack of awareness, shortened attention span, sleep disturbance and altered mood
2. asterixis may be present

GRADE 2

1. lethargy, disorientation to time, amnesia to recent events, impaired simple computations, inappropriate behaviour, slurred speech
2. asterixis is present

GRADE 3

1. Somnolence, confusion, disorientation to place, bizarre behaviour, clonus, nystagmus and positive Babinski sign.
2. Asterixis is usually absent.

GRADE 4

1. Coma, lack of verbal eye and oral response

It is characterized by subtle and sometimes intermittent changes in memory, personality, concentration, and reaction times. [42]. Early changes are subclinical - termed *minimal hepatic encephalopathy* (MHE)—most often recognized only in retrospect. MHE is clinically significant because studies of compensated cirrhotic patients without clinical evidence of HE indicate that more than one half perform abnormally on number connection tests or auditory-evoked responses, and more than one half may be unfit to drive an automobile, as assessed by a battery of psychometric tests. [43]

When encephalopathy progresses, the neurologic abnormalities become more apparent and commonly are graded on a numerical scale that reflects increasing degrees of neurologic dysfunction. Stage 1 encephalopathy is characterised by involvement of higher cortical functions, with decreases in attention span, changes in personality, irritability, and impaired computational and construction skills. There is also a change in the sleep pattern with wakefulness at night and drowsiness during the day. The EEG tracing may show subtle slowing of the dominant frequency.

Progression to stage 2 encephalopathy is characterized by more drowsiness and lethargy, and by the appearance of movement disorders that reflect increasing involvement of the descending reticular system or other neurologic structures. These movement disorders include tremors, incoordination, and asterixis. [44] In cooperative

patients, asterixis is commonly evaluated by asking the patient to hold the arms extended with the wrists dorsiflexed; an abrupt loss of flexor tone and a characteristic wristdrop occur in a periodic manner every 2 to 3 seconds. Alternatively, the periodic relaxations become apparent when the examiner grips the patient's hand and holds the wrist lightly in a dorsiflexed position. In a patient with mental confusion, drowsiness, and personality changes, the presence of asterixis is highly suggestive of underlying hepatic encephalopathy. An EEG performed in stage 2 usually shows slower rhythms and the appearance of triphasic waves in the frontal regions.

Progression to stage 3, defined as increasing obtundation in a still arousable patient, or to stage 4, in which the patient is comatose, reflects either severe bilateral cortical dysfunction or involvement of the brainstem and reticular activating system. Asterixis may be lost, and hyperreflexia and muscle rigidity become apparent. The EEG shows severe slowing, with frequencies in the theta and delta ranges. Even though the clinical features may be fully reversible with treatment (see later), encephalopathy of this degree generally is a manifestation of advanced liver disease and is associated with a poor long-term prognosis

Hepatic encephalopathy manifests as a spectrum of neurologic abnormalities, but each of the individual principal clinical features is nonspecific. Subtle impairments of memory, consciousness, and personality are easily overlooked if the underlying liver disease is not recognized. Alternatively, even if well-defined periods of encephalopathy have been documented, it may be difficult to assess whether recovery has been complete. By contrast, the clinical features of advanced encephalopathy and asterixis in a patient with known cirrhosis and portal hypertension are quite characteristic, and the combination

of asterixis, hyperammonemia, and other clinical features permits confident recognition of portosystemic encephalopathy.

The recognition of MHE is of particular importance in view of the prevalence of cirrhosis. In the absence of characteristic features, subtle abnormalities of neuropsychiatric function generally are assessed by more specialized neuropsychiatric tests such as the trail-making test, block design and digit symbol tests, and visual reaction times. [45] In addition, some evidence supports the use of brainstem auditory-evoked responses and somatosensory-evoked responses for the diagnosis of HE. [46] Some of these specialized tests are not readily performed in the clinical setting. Therefore, outside of the research setting, a high index of suspicion in patients at risk of HE, such as those with a recent surgical or transjugular portosystemic shunt, [47] and a beneficial response to a therapeutic trial are clinically more useful diagnostic approaches.

Special attention has been paid to the cerebral functional defects of latent or subclinical HE with regard to the patient's fitness to drive and quality of life. Driving requires complex response and spatial recognition skills, and in a series of cirrhotic patients without clinical signs of portosystemic encephalopathy, psychometric testing indicated that 60% were unfit to drive and an additional 25% had questionable driving skills. Some, but not all, studies have confirmed a reasonably high frequency of subclinical encephalopathy in patients with cirrhosis, but no consensus has been reached on whether the ability to drive is significantly impaired in the absence of major abnormalities on neuropsychiatric testing. [48] Therefore, decisions regarding driving should be made on a case-by-case basis, with no clear support to strictly prohibit driving in patients with compensated cirrhosis and no overt evidence of encephalopathy.

Administration of lactulose does seem to be beneficial in improving psychometric performance.

Progression to clinically apparent HE is commonly associated with two modes of presentation. Encephalopathy may be acute in onset, with rapid deterioration of mental function and coma in the absence of previous symptomatology, or chronic and relapsing, as usually occurs in patients with more pronounced portal hypertension. In either case, HE typically is reversible, and a precipitating cause for the deterioration usually can be identified and corrected. The relative contributions of different precipitating factors were analyzed by Fessel and Conn in 100 patients requiring hospitalization and are illustrated in the figure below. Many of these precipitating factors are readily understood on the basis of their effects on ammonia. An increase in nitrogenous substances as a result of azotemia and gastrointestinal hemorrhage together accounted for almost one half of the admissions. Medications also figured prominently, and causative mechanisms for the precipitation of coma were either direct, from increased sensitivity to tranquilizers and sedatives, or indirect, through hypokalemia, dehydration, and alkalosis associated with diuretic use. Identification and correction of these causes constitute the cornerstone of effective therapy, and in very few patients with chronic cirrhosis is encephalopathy the result of an irreversible loss of hepatocyte mass and synthetic capacity.

Table 1 COMMON CLINICAL FACTORS THAT MAY PRECIPITATE HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

Nitrogenous Encephalopathy	Non-Nitrogenous Encephalopathy
Uremia/azotemia	Sedatives, benzodiazepines
Gastrointestinal bleeding	Barbiturates
Dehydration	Hypoxia
Metabolic alkalosis	Hypoglycemia
Hypokalemia	Hypothyroidism
Constipation	Anemia
Excessive dietary protein	
Infection	

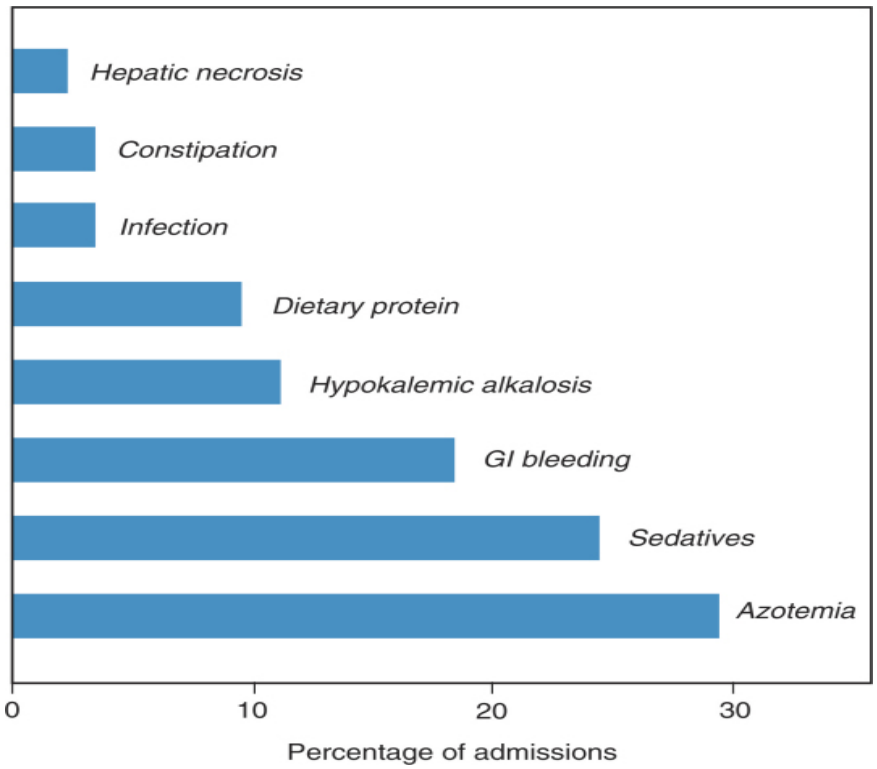


Fig 2 Clinical causes of hepatic encephalopathy. GI, gastrointestinal. *(From Fessel JM, Conn HO: An analysis of the causes and prevention of hepatic coma. Gastroenterology 62:191, 1972.)*

Blood ammonia levels may be measured when hepatic encephalopathy is suspected, both for diagnostic purposes and as a general guide to treatment. Normal ammonia values do not exclude the diagnosis and should not delay initiation of ammonia-lowering therapy. Measurable differences exist between arterial and venous levels of ammonia. In practice, venous levels are measured most often for convenience and because no evidence is available to suggest that the accuracy of measurement or outcome of the patient depends on the source of the blood sample. Approximately one fourth of patients will have non-nitrogenous precipitants of encephalopathy, such as adverse reactions to sedatives and fluid and electrolyte imbalances. In view of the potential involvement of the GABA receptor complex and the abnormalities in multiple other signalling pathways in HE, it is not surprising that patients with normal ammonia values respond to treatment in a manner similar to those with elevated ammonia levels. Measurement of glutamine levels in the cerebrospinal fluid and an EEG can provide confirmation of the clinical impression of HE but are neither sensitive nor specific.

The clinical stages of HE provide a general index of severity in the acute setting but are not sufficiently quantitative to assess subtle changes in clinical performance. Consequently, the need remains for a reliable, reproducible test that can be easily administered. The trail-making test provides a semi quantitative measure of encephalopathy. In this test, the subject connects 25 consecutively numbered circles, and the number of seconds required to complete the task is recorded [49] An alternative figure-making test also has been introduced and validated for patients who cannot recognize numbers, and detects subclinical encephalopathy in 48% of subjects. [50] None of these measures alone is entirely satisfactory, and they are best utilized when administered serially to assess changes over time. The overall assessment provided by the Portosystemic Encephalopathy Index introduced by Conn in the 1970s and based on an

arbitrary measure of the degree of abnormality of five factors—clinical assessment of mental state, trailmaking time, EEG, asterixis, and arterial ammonia—is still unsurpassed as a clinical research tool. Although complex, the Index emphasizes the need for taking multiple parameters into account in the overall assessment and diagnosis of HE.

In the near future, the diagnosis of HE is likely to include cerebral imaging studies as well. Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are used to exclude structural causes of altered mental status such as intracerebral bleeding. However, MRI and ^{1}H spectroscopy of the brain of patients with cirrhosis detect abnormalities in brain metabolites that correlate with encephalopathy and are completely reversed 3 to 7 months after liver transplantation. [51] The overall sensitivity of these and other techniques is not yet established, but they offer promise for real-time imaging of encephalopathy-specific brain metabolic changes in the future.

The principles involved in management of HE are straightforward: identify and correct the precipitating cause(s), initiate ammonia-lowering therapy, and minimize the potential medical complications of cirrhosis and depressed consciousness. Among these, careful scrutiny for and correction of the underlying cause of the deterioration, such as bleeding, tranquilizers, electrolyte abnormalities, or azotemia, is the most important. These basic steps are relatively easy and effective, with excellent recovery to basal function in most patients when comorbid factors are absent.

Correction of the precipitating factor for encephalopathy depends on a careful review of potential contributors, many of which, such as gastrointestinal bleeding, dehydration, hypokalemia, and azotemia, are readily apparent from the initial physical examination and basic laboratory studies. Particular attention should be paid to the possibility of gastrointestinal bleeding because of the high risk of bleeding in the setting

of portal hypertension and the need for specific therapeutic intervention. Catabolism of blood in the intestine liberates ammonia and presumably benzodiazepine receptor ligands and other mediators and is a classic cause of nitrogenous encephalopathy.

Action should be taken as soon as potential precipitating factors are identified. If azotemia is the cause, rehydration with concomitant attention to other pre-renal factors is indicated. If bleeding is the precipitant, it must be controlled. Medications should be reviewed in detail, with specific attention to tranquilizers and sedatives and to the adverse effects of diuretics. Any potentially contributing medicines should be discontinued. Moreover, general measures to correct and maintain serum glucose levels, oxygenation, and acid-base balance are essential.

The second step in treatment involves measures directed at lowering elevated blood ammonia levels. Therapy involves removing the source of the ammonia from the intestinal tract, trapping ammonia in the colon to prevent systemic absorption, and, in some patients, decreasing the number of ammonia-producing bacteria in the colon. In patients with gastrointestinal bleeding, removing the source of ammonia involves eliminating blood from the gastrointestinal tract. For haemorrhage in the upper gastrointestinal tract, nasogastric lavage to remove blood and initiation of lactulose or other cathartics to speed transit through the colon are appropriate. In patients with more chronic encephalopathy that is not associated with bleeding, excessive ingestion of protein or constipation may elevate blood ammonia to levels high enough to cause encephalopathy. In such cases, dietary protein intake should be decreased to approximately 60 g per day, and lactulose or other laxatives should be prescribed to eliminate protein from the colon. In addition, substitution of vegetable protein for other protein sources appears to be of some advantage, because of a lower rate of ammonia

production with such foods. [52] In severe encephalopathy, dietary protein should be eliminated completely until the patient improves sufficiently to allow institution of a stable therapeutic regimen.

The synthetic disaccharides lactulose (1, 4-galactosidofructose) and lactitol (beta-galactosidosorbitol) have been the mainstays of medical therapy of nitrogenous hepatic encephalopathy for decades. Debate continues as to their efficacy, however. These agents target the production and absorption of ammonia and benzodiazepine receptor ligands in the gut. Lactulose was introduced in the 1970s as an agent for therapy of HE on the basis of the concept that the drug would acidify the contents of the colon, thereby favouring trapping of NH_4^+ in the lumen and prevention of absorption. In the colon, lactulose is metabolized by bacteria to release lactic, acetic, and other organic acids and decreases stool pH to approximately 5.5. In most relevant studies, treatment with lactulose is clinically effective in greater than 80% of patients, in whom serum ammonia levels decrease and the encephalopathic changes abate (including patients with subclinical encephalopathy revealed by psychometric testing).Treatment with lactulose is well tolerated, and the principal toxic effects are abdominal cramping, diarrhea, and flatulence. When administered orally to normal adults in amounts up to 160 g per day, lactulose decreases faecal ammonia production and increases faecal nitrogen excretion approximately four-fold, as a result of an increase in stool volume. An increase in the number of bowel movements to two to four soft stools per day is an important therapeutic goal. In comparative clinical trials, lactulose and lactitol have been equally effective, but a trend toward better palatability and fewer side effects with lactitol has been observed. Over longer periods in the outpatient setting, evidence suggests that efforts to modulate colonic bacterial flora to increase the proportion on non-urease producing *Lactobacillus* species can lower blood ammonia levels, with subsequent abatement of encephalopathy

Several antibiotics, including neomycin, ampicillin, and rifaximin, also are effective in lowering blood ammonia levels. [53] The effect of these antibiotics on ammonia is the result in large part of a decrease in the number of colonic bacteria and a concomitant decrease in bacterial urease and protease activity, the main enzymes responsible for generation of ammonia. In addition, decreasing colonic bacteria appears to decrease the production of benzodiazepine receptor ligands. [54] In most patients, the response to antibiotics is equivalent to that of lactulose, and in small series, use of antibiotics has been associated with improved patient compliance. Nonspecific use of antibiotics in the absence of an established or suspected infection raises concerns, however. For example, neomycin can be absorbed systemically in concentrations sufficient to induce ototoxicity and nephrotoxicity, particularly when the drug is given over long periods. Furthermore, the alterations in gut flora associated with antibiotic use can contribute to diarrhoea, malabsorption, and staphylococcal and other bacterial overgrowth syndromes. Therefore, chronic therapy with antibiotics should be reserved for patients who cannot tolerate oral lactulose or lactitol therapy, and neomycin should be avoided.

The relative benefit of nonabsorbable disaccharides as compared with antibiotics for acute HE has been evaluated in a review of 22 randomized clinical trials. Although effective alone, lactulose and lactitol were not as effective as antibiotics, but it was unclear whether the difference was clinically important.

Treatment of HE in the absence of elevated blood ammonia levels follows the same principles as those for nitrogenous HE, including a careful review of the patient's use of sedatives and analgesics. Prolonged recovery from sedatives given for endoscopy or other procedures is characteristic of patients with HE. Therapy to lower blood

ammonia levels appears to be effective in these patients, perhaps because of the effects on GABA-ergic transmission.

The role of flumazenil and other benzodiazepine receptor antagonists is not yet defined. In clinical trials, evidence for [55] and against a clinical benefit with these agents has been presented. Even when the response was favourable, the recovery was rarely complete and was short-lived because of the pharmacokinetic properties of the drug. A review of 13 trials concluded that the short-term beneficial effect was not associated with significant improvement in the rates of recovery and mortality. [56] Much remains to be learned regarding the origin, overall contribution, and therapy of increased GABAergic transmission in HE. At present, as suggested by Jones and others, therapy with flumazenil should be limited to (1) reversing the effects of exogenous benzodiazepines; (2) aiding in the differential diagnosis of encephalopathy; and (3) providing information about prognosis in HE. These indications are likely to evolve with additional clinical experience and the development of more selective and effective benzodiazepine receptor analogs.

There is a long history of clinical trials involving other more experimental approaches to the treatment of HE. These approaches have included use of levodopa, branched-chain amino acids, charcoal hemoperfusion, and molecular adsorbents. [57] Although anecdotal reports have been encouraging, none of these therapies has been sufficiently beneficial to lead to widespread application.

MATERIALS AND METHODS

MATERIALS AND METHODS

This cross-sectional study was carried out in the Department of Medical Gastroenterology, Madras Medical College, Chennai. This is the major referral tertiary care center available to the population of Tamilnadu, Pondicherry, and neighbouring states Andhra Pradesh and Karnataka. The main aim of this study was to non-invasively observe the cerebral hemodynamics in patients with liver cirrhosis and to determine the role of cerebral hemodynamics in the causation of hepatic encephalopathy. The study was carried between the periods of January 2009 to December 2009 (12 months)

Fifty patients with cirrhosis were included. Twenty-five with and without encephalopathy in each group.

Inclusion criteria

Patients with clinical diagnosis of hepatic cirrhosis with and without hepatic encephalopathy admitted to the department of Medical Gastroenterology, Madras Medical College, Chennai.

The diagnosis of cirrhosis is based on typical clinical findings (shrunken liver, signs of portal hypertension like splenomegaly, ascites etc) characteristic features by using ultrasonography or computed tomography and supporting biochemical data.

Clinical encephalopathy is graded based on West Haven criteria.

Table 2 Clinical Stages of Hepatic Encephalopathy

	Impairment	
Clinical Stage	**Intellectual Function**	**Neuromuscular Function**
Subclinical	Normal examination findings, but work or driving may be impaired	Subtle changes on psychometric or number connection tests
Stage 1	Impaired attention, irritability, depression, or personality change	Tremor, incoordination, apraxia
Stage 2	Drowsiness, behavioral changes, poor memory and computation, sleep disorders	Asterixis, slowed or slurred speech, ataxia
Stage 3	Confusion and disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, and muscular rigidity
Stage 4	Stupor and coma	Dilated pupils and decerebrate posturing; oculocephalic ("doll's eye") reflex; absence of response to stimuli in advanced stages

Exclusion criteria

1. Recent alcohol intake.
2. Cerebrovascular disease.
3. Cardiac disease.
4. Peripheral vascular disease.
5. Chronic pulmonary disease.

Protocol

1. All patients who met the above criteria were included in the study and got admitted in our department. The following were noted in each patient
2. Age
3. Sex
4. Presenting complaint
5. Precipitating factors for encephalopathy (gastrointestinal bleed, constipation, azotemia, infection, hypokalemia, sedatives, others)
6. Personal history – alcohol intake (duration and quantity)
7. Vital data – heart rate and blood pressure

8. A thorough physical examination was done in all the patients. Signs of chronic liver disease with portal hypertension like palmar erythema, spider naevi, gynaecomastia, fetor hepaticus, and asterixis were noted. Abdominal examnation was done. Encephalopathy was graded according to West Haven criteria.

Investigations

The following investigations were done in patients with cirrhosis (30 patients)

1. Liver function tests
2. Renal function tests
3. Prothrombin time / INR
4. Viral markers (HBsAg, Anti-HCV)
5. Ultrasound of the abdomen/ Computed tomography (some patients)
6. Diagnostic upper GI endoscopy
7. Stage of liver disease assessed based on Child-Turcotte-Pugh classification

Table 3 CHILD-TURCOTTE-PUGH CLASSIFICATION

	Numerical Score		
Parameter	**1**	**2**	**3**
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Slight/moderate	Moderate/severe
Bilirubin (mg/dL)	<2.0	2-3	>3.0
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds increased)	1-3	4-6	>6.0
Total Numerical Score	**Child-Turcotte-Pugh Class**		
5-6	A		
7-9	B		
10-15	C		

Measurement of cerebral hemodynamics

After the subjects had rested for half-an-hour in supine position in a quiet room, the measurement of cerebral hemodynamics were carried out by the same observer by using a Duplex Doppler apparatus with color Doppler sonographer (Fig 3a) and a Transcranial Doppler probe (SIEMENS ACUSON Antares). The right middle cerebral artery was identified through the temporal ultrasound window with color Doppler ultrasonography (Fig 3b). The pulsatility index and resistive index were automatically calculated according to the following formulas:

Pulsatility index = (peak systolic velocity – end-diastolic minimum velocity)/mean velocity;

Resistive index = (peak systolic velocity – end-diastolic minimum velocity)/ peak systolic velocity.

To minimize measurement error, each result is expressed as mean of two measurements.

Statistical analysis:

All values are expressed as the mean±SD. Statistical analysis of the results was conducted by using analysis of variance (ANOVA), t-test and Chi-square tests. Correlation analysis was carried out by using univariate linear regression analysis. To identify independent factors predictive of transcranial Doppler parameters, multiple regression analysis was performed. A $P<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software version 15.0.

Figure 3a Siemens Acuson Antares Doppler Ultrasound apparatus

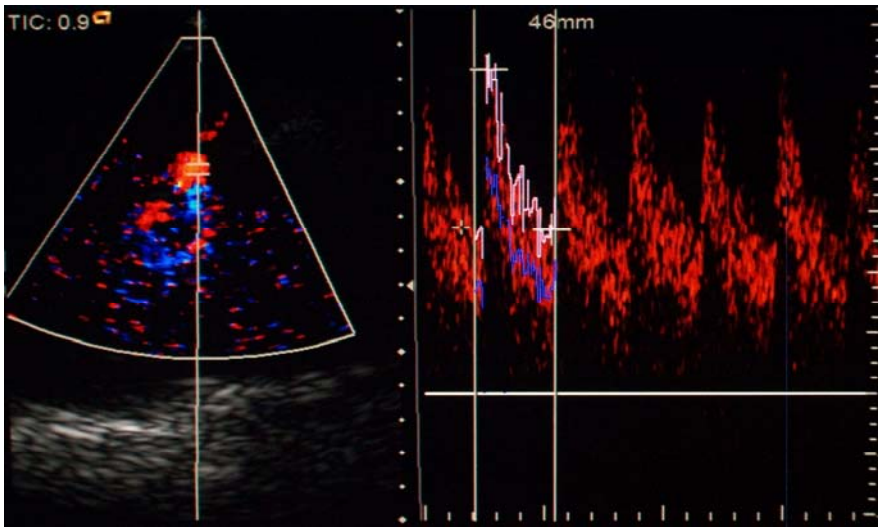


Fig 3b Photograph showing sampling volume positioned within middle cerebral artery and time-velocity waveform

Statistical analysis:

All values are expressed as the mean±SD. Statistical analysis of the results was conducted by using analysis of variance (ANOVA), t-test and Chi-square tests. Correlation analysis was carried out by using univariate linear regression analysis. To identify independent factors predictive of transcranial Doppler parameters, multiple regression analysis was performed. A $P<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software version 15.0.

RESULTS

RESULTS

The clinical data for the subjects are shown in Table 4

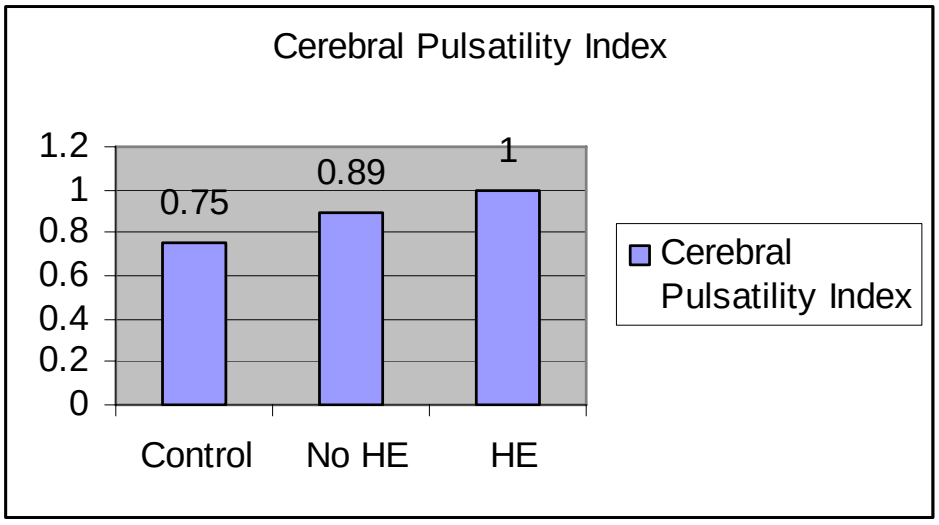
Table 4

CHARACTERISTICS OF 45 PATIENTS IN THIS STUDY

Variable	Normal range	Controls (n=15) Mean±SD	Cirrhosis. No HE (n=15) Mean±SD	Cirrhosis. HE. (n=15) Mean±SD
Age (yr)	-	47.40±6.36	48.53±6.22	48.13±6.10
Gender (M/F)	-	15/0	15/0	15/0
MBP (mm Hg)	-	87.67±1.67*	86.60±5.30*	82.67±5.23
Heart rate (bpm)	-	82.27±3.01	84.13±6.02	86.00±6.18
Bilirubin (mg/dL)	0.2-1.2	0.76±0.11*	1.64±1.43	3.78±4.57
Albumin (g/dL)	3.5-5.0	3.88±0.34	3.50±0.27#	3.20±0.40#
AST (IU/L)	<40	29.33±3.90*	43.07±27.98	55.07±29.97
PT	11.1-13.1s	1.05±0.05	1.34±0.24#	1.42±0.30#

*P<0.05 compared with HE group #P<0.05 compared with control

Fig 4 Cerebral Pulsatility index in controls and patients with cirrhosis



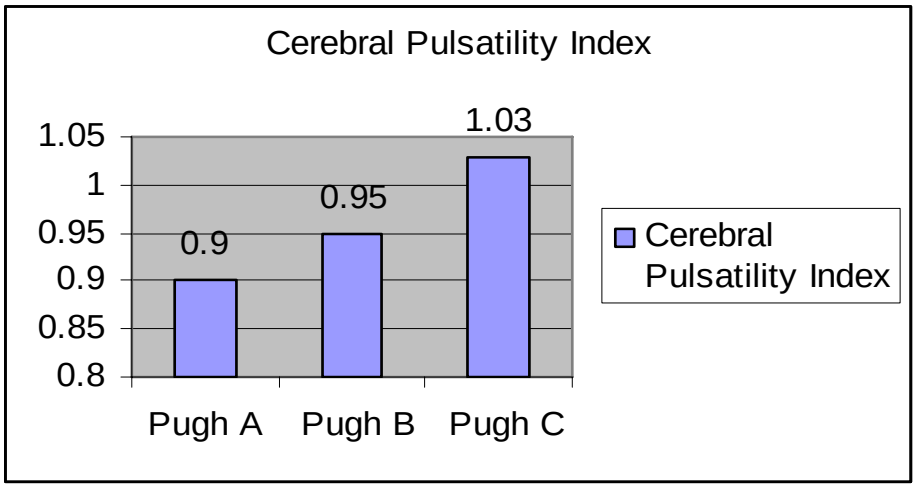
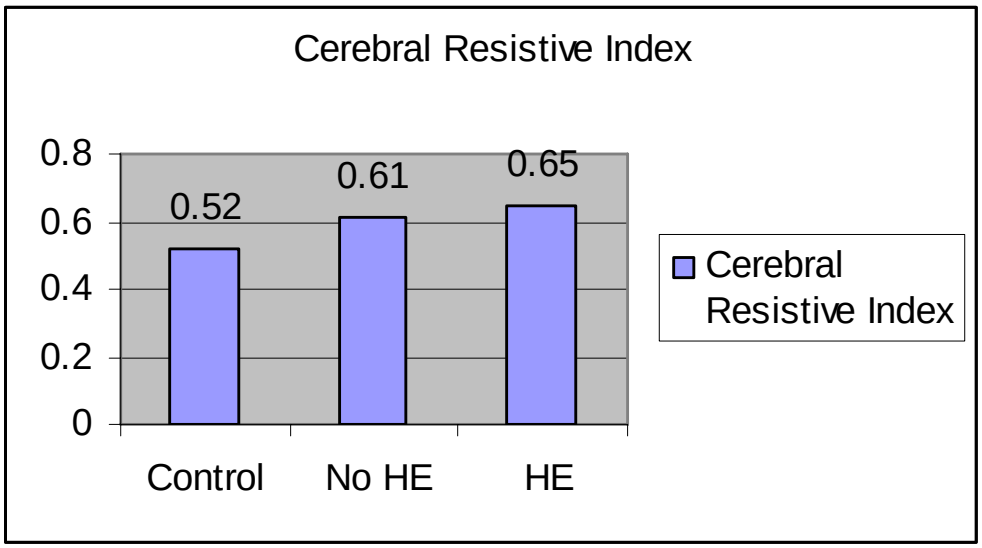
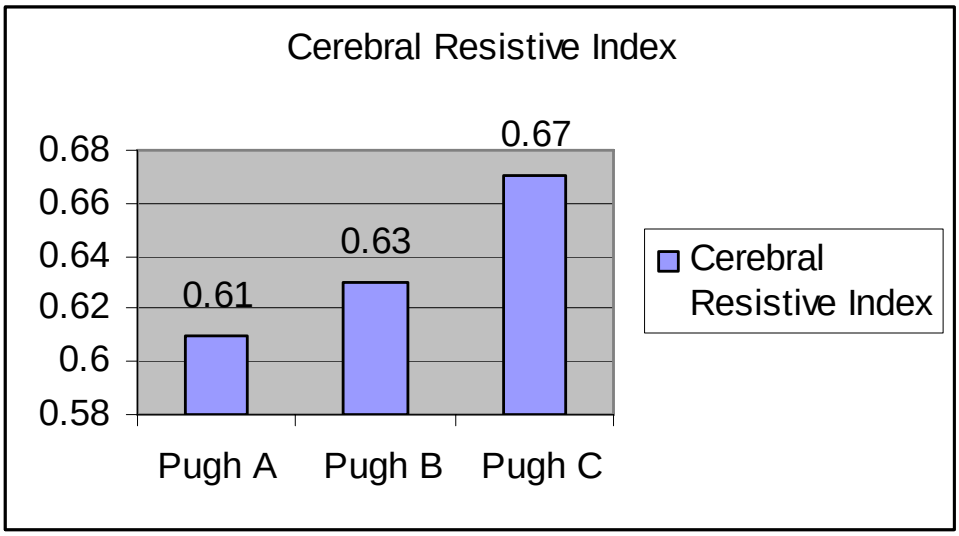


Fig 5 Cerebral Resistive index in controls and patients with cirrhosis





Pulsatility and resistive indices of the right middle cerebral artery in all subjects are shown in fig 4 and 5 and tabulated in tables 6 and 7.

Table 6

Multiple Comparisons

Dependent Variable: PI
Tukey HSD

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Control	No HE	-.13733*	.02670	.000	-.2022	-.0725
	HE	-.25067*	.02670	.000	-.3155	-.1858
No HE	Control	.13733*	.02670	.000	.0725	.2022
	HE	-.11333*	.02670	.000	-.1782	-.0485
HE	Control	.25067*	.02670	.000	.1858	.3155
	No HE	.11333*	.02670	.000	.0485	.1782

*. The mean difference is significant at the .05 level.

Table 7

Multiple Comparisons

Dependent Variable: RI
Tukey HSD

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Control	No HE	-.08467*	.01229	.000	-.1145	-.0548
	HE	-.12867*	.01229	.000	-.1585	-.0988
No HE	Control	.08467*	.01229	.000	.0548	.1145
	HE	-.04400*	.01229	.003	-.0739	-.0141
HE	Control	.12867*	.01229	.000	.0988	.1585
	No HE	.04400*	.01229	.003	.0141	.0739

*. The mean difference is significant at the .05 level.

Significant differences in cerebral pulsatility and resistive indices were found among these three groups (ANOVA: $F = 44.19$, $P<0.001$ for pulsatility index; $F = 56.60$, $P<0.001$ for resistive index). The cerebral pulsatility in patients with hepatic

encephalopathy (HE) (1.00±0.01) was higher than those without HE (0.89±0.05) and controls (0.75±0.04). Similarly, the resistive index in patients with HE (0.65±0.04) was higher than those without HE (0.61±0.03) and controls (0.52±0.01).

The cerebral resistive index in child C was found to be higher (0.67±0.06) compared to child A (0.61±0.04). Similar trend was not observed for pulsatility index.

These cerebral hemodynamic parameters (Pulsatility and Resistive indices) were compared with the results of clinical laboratory tests in patients with liver cirrhosis (Table 8). With univariate analysis the pulsatility and resistive indices were significantly correlated with mean blood pressure, bilirubin and albumin. Multivariate analysis showed that only bilirubin was significant independent predictor of cerebral pulsatility index (Table 9)

Table 8

Relationship of cerebral pulsatility and resistive indices with clinical laboratory test results in patients with liver cirrhosis

		Pulsatility Index		Resistive Index	
	N	R	P	R	P
Heart Rate	30	0.16	NS	0.17	NS
Mean BP	30	-0.42	0.01	-.0.552	0.002
Bilirubin	30	0.612	0.00	0.551	0.002
Albumin	30	-.0.50	0.005	-0.43	0.017
AST	30	0.13	NS	0.21	NS
PT	30	0.44	0.013	0.26	NS

Table 9

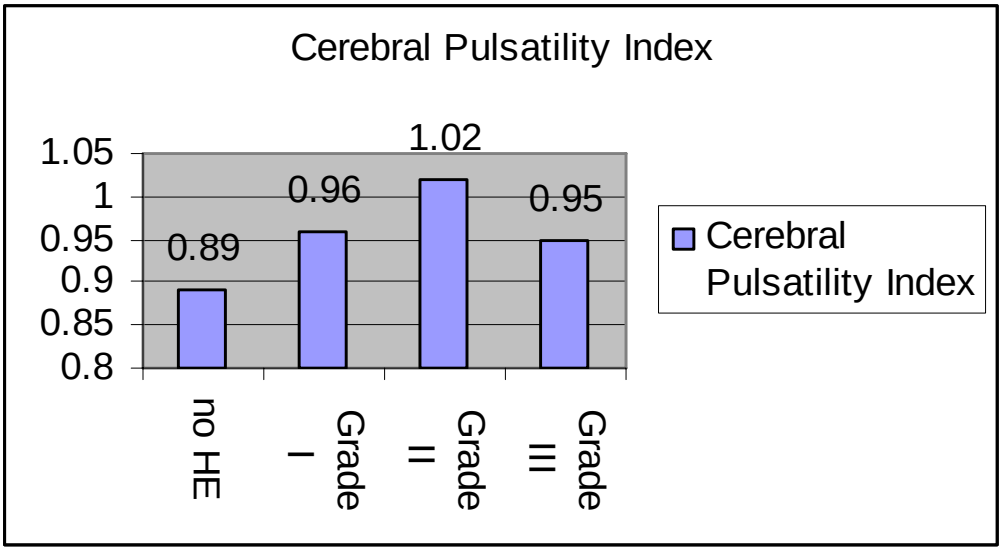
Multivariate analysis of the relationships among laboratory tests with cerebral pulsatility and resistive indices in patients with liver cirrhosis

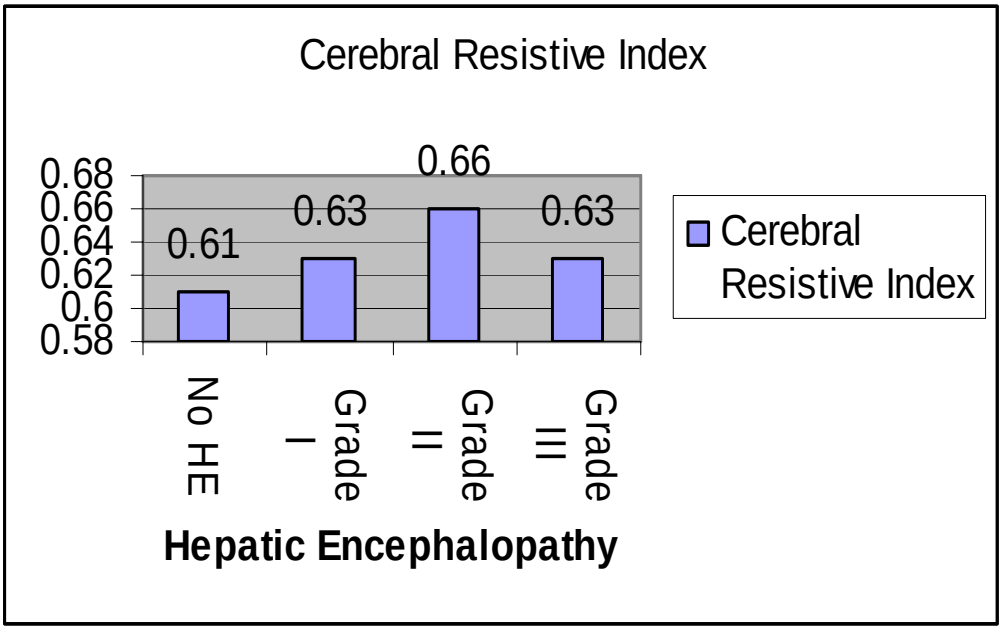
	PI			RI		
Variables	Regression coefficient	SE	P value	Regression coefficient	SE	P value
MBP	-.002	0.003	0.504	-.003	0.001	0.057
BIL	0.01	0.006	0.029	0.005	0.003	0.085
ALB	-.043	0.054	0.431	-.004	0.024	0.872

Pulsatility index, correlation coefficient (R) = 0.641, R^2 = 0.410; resistive index, correlation coefficient (R) = 0.639, R^2 = 0.408;

Fifteen of the patients with cirrhosis had clinical hepatic encephalopathy (HE; grade of I-III; Fig 6). The cerebral pulsatility index was higher in patients with grade II encephalopathy (1.02±0.11) compared with patients without HE (0.89±0.05). The cerebral resistive index was also higher in patients with grade II encephalopathy (0.66±0.04) compared with patients without encephalopathy (0.61±0.03). Similar observation was not seen with other grades of encephalopathy. Also, significant differences by ANOVA in cerebral pulsatiliity (F = 5.01, P = 0.007) and resistive indices (F = 4.05, P = 0.017were found among the three subgroups of HE.

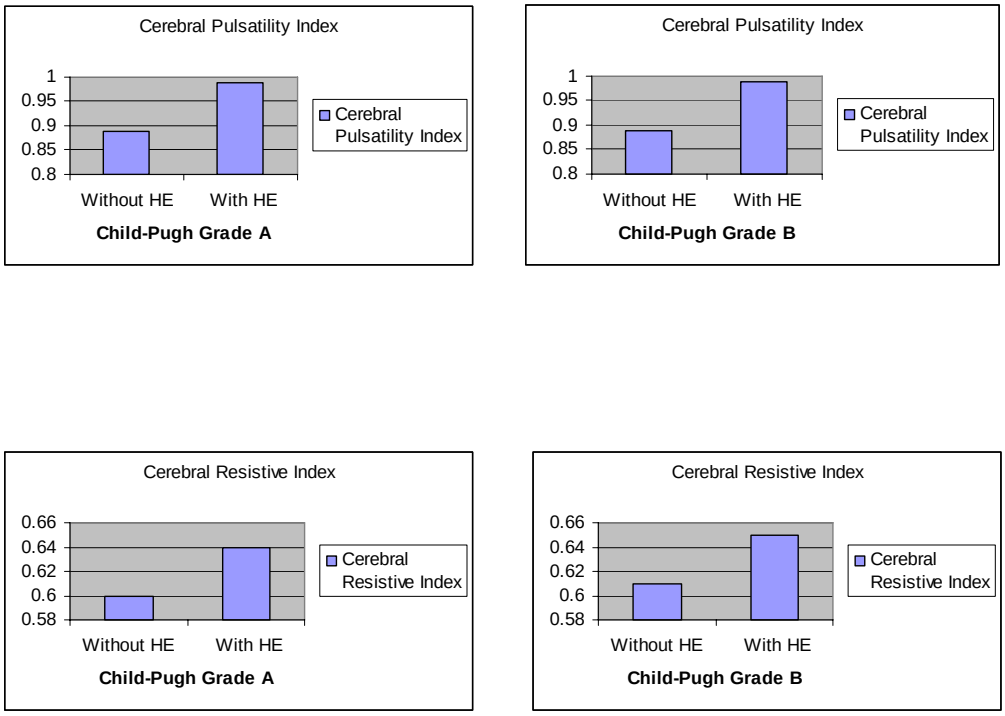
Fig 6


Cerebral Pulsatility Index
1.05
1
0.95
0.9
0.85
0.8
0.89
0.96
1.02
0.95
no HE
Grade I
Grade II
Grade III
Cerebral Pulsatility Index


Cerebral Resistive Index
0.68
0.66
0.64
0.62
0.6
0.58
0.61
0.63
0.66
0.63
No HE
Grade I
Grade II
Grade III
Hepatic Encephalopathy
Cerebral Resistive Index

To find out whether the presence of hepatic encephalopathy influences the cerebral hemodynamics in cirrhotics patients, TCD parameters were compared between cirrhotic patients with and without encephalopathy with the same Child-Pugh grade (fig 7). The cerebral pulsatility index in patients with hepatic encephalopathy (0.99±0.06) was higher than that in patients without HE (0.89±0.06) in the Child-Pugh grade B. similarly the resistive index was also higher (0.65±0.02) in those with HE compared to those without HE (0.61±0.02) in the Child-Pugh grade B.

Fig 7



DISCUSSION

DISCUSSION

Cerebral blood flow (CBF) is found to be reduced in patients with cirrhosis. Compared to healthy volunteers, intravenous injection of ^{133}Xenon in cirrhotic patients revealed reduced CBF. [58] Cerebral blood flow in cortical areas is also decreased in patients with alcoholic cirrhosis. [59] Similar reduction in CBF was found in alcoholic and non- alcoholic cirrhosis patients by single photon emission computed tomography (SPECT) compared to controls. [60]

Guevera *et al* have measured the cerebral resistive index (RI) instead of CBF in cirrhotic patients and demonstrated that RI is higher in cirrhotics with ascites compared to controls. [4] Cerebral pulsatility index (PI) and resistive index (RI) are more accurate than cerebral blood velocity as indicators of cerebral vascular resistance.

In this study, both pulsatility and resistive indices of the middle cerebral artery were significantly higher in cirrhotic patients compared to controls. These results were in agreement with those of Guevera *et al.* Patients with Child-Pugh C had higher RI compared to Child-Pugh A indicating that the cerebral resistance (RI) increased with the severity of liver cirrhosis. Though the pulsatility and resistive indices were significantly correlated with mean blood pressure, bilirubin and albumin, multivariate analysis showed that only bilirubin was significant independent predictor of cerebral pulsatility index and therefore the cerebral resistance. Cerebral resistance changes in parallel with the changes of cerebral perfusion pressure, and maintains a constant CBF under autoregulation. [61] Elevated cerebral vascular resistance in early cirrhosis is attributed to expanded total blood volume by compensated abnormal renal sodium handling of pre-ascitic stage. [62] Similar increase in decompensated cirrhosis may be caused by an overactivation of the rennin-angiotensin-aldosterone system and the sympathetic nervous system secondary to increasing systemic arterial vasodilatation. Advanced cirrhotic patients often exhibit

impaired cerebral autoregulation. Larsen *et al* reported that the autoregulation is functionally lost in some cirrhotics. [63] Therefore, in the advanced cirrhotic patients with high cerebral resistance, systemic hypotension may result in cerebral hypoperfusion under impaired autoreulation.

To find out whether the presence of hepatic encephalopathy is related to the cerebral vascular resistance, we compared cerebral PI and RI in patients with and without encephalopathy with the same Child-Pugh grade. The cerebral pulsatility and resistive indices in patients with hepatic encephalopathy was higher than that in patients without HE in the Child-Pugh grade B. The cerebral pulsatility and resistive indices were higher in patients with grade II encephalopathy compared with patients without HE. Similar observation was not seen with other grades of encephalopathy Almdal *et al* and Rodriguez *et al* [64] have also reported that CBF decreases in patients with hepatic encephalopathy or with subclinical hepatic encephalopathy. Hepatic encephalopathy is clearly related to increased cerebral vascular resistance. These findings indicate that cerebral vascular resistance may reflect reversible functional changes rather than irreversible anatomic damage.

CONCLUSION

CONCLUSION

Cerebral pulsatility and resistive indices of the middle cerebral artery are significantly higher in cirrhotic patients compared to controls indicating higher cerebral vascular resistance in cirrhotic patients.

Patients with Child-Pugh C have higher resistive index compared to Child-Pugh A indicating that the cerebral resistance (RI) increases with the severity of liver cirrhosis.

Serum bilirubin significantly correlates with cerebral pulsatility index and therefore the cerebral resistance.

The cerebral pulsatility and resistive indices are higher in patients with hepatic encephalopathy compared to patients without encephalopathy.

The cerebral pulsatility and resistive indices are higher in patients with grade II encephalopathy compared with patients without encephalopathy. Hence hepatic encephalopathy is clearly related to the cerebral vascular resistance and could play a role in its pathogenesis.

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APPENDIX

No.	

STUDY ON CVR USING TCD

PROFORMA

Name: **Age/Sex**: **IP No**:

Address: **Phone No:**

Ward

Presenting complaints: **Duration**:

Encephalopathy : Grade I / II / III / IV

Precipitating factors :	**Yes/No**	**Details**
1) Azotemia :		
2) Infection :		
3) Hypokalemia/alkalosis:		
4) Constipation :		
5) GI bleed :		
6) Excess dietary protein :		
7) Sedatives :		
8) Others :		

Personal History:

Alcohol intake : Yes/No Duration:

Amount:

Examination :

Vital data :

Heart Rate :

Blood pressure (mean) :

Signs of CLD: Spider nevi/ parotid enlargement/ gynecomastia/ testicular atrophy/ sparse axillary hair / Dupuytren contracture

Abdomen: **Details:**

Liver

Spleen

Free fluid : Minimal/ Moderate/ Tense

Tenderness: Present/ Absent

Investigations:

TC DC: N/L/E:

Platelet count: ESR:

LFT :

RFT :

PT/INR :

HBsAg/Anti HCV :

Upper GI endoscopy:

USG abdomen: **CT Abdomen:**

Liver:

Spleen:

PV:

Free fluid:

CHILD CLASS: Encephalopathy/ Ascites/ Albumin/ STB/ PT: **A / B / C**

TCD:	**VALUE 1**	**VALUE 2**	**MEAN**
PI			
RI			

CONSENT FORM

Title of Project:

Name of Researcher:

	Please tick to confirm
I confirm that I have read and understand the information provided to me for the above study.	☐
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I agree to take part in the above research study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

MASTER CHART – CONTROLS

S NO	AGE	SEX	HR	MBP	BIL	AST	ALB	PT	PI	RI
1	43	M	80	88	0.9	30	3.5	1.1	0.64	0.56
2	45	M	78	86	0.8	32	3.5	1.0	0.76	0.53
3	42	M	82	90	0.8	28	4.0	1.0	0.74	0.52
4	40	M	84	88	0.7	26	4.2	1.1	0.76	0.53
5	60	M	80	90	0.9	28	4.4	1.0	0.77	0.51
6	53	M	86	86	0.9	30	4.5	1.1	0.78	0.50
7	45	M	84	86	0.7	32	4.0	1.0	0.78	0.53
8	43	M	82	87	0.6	34	3.8	1.1	0.79	0.55
9	45	M	80	88	0.7	28	3.6	1.1	0.80	0.54
10	50	M	88	86	0.6	30	3.5	1.0	0.79	0.55
11	57	M	82	86	0.6	34	4.2	1.1	0.78	0.52
12	43	M	84	90	0.7	36	4.0	1.0	0.76	0.53
13	50	M	86	88	0.9	22	3.8	1.1	0.74	0.52
14	40	M	78	90	0.8	24	3.8	1.0	0.71	0.51
15	55	M	80	86	0.8	26	3.4	1.1	0.77	0.53

MASTER CHART
CIRRHOSIS WITHOUT HEPATIC ENCEPHALOPATHY

S no	age	sex	Alcohol	HR	MBP	BIL	AST	alb	PT	Cr	Child	PI	RI
1	44	M	N	76	83	4.7	45	3.2	2.12	0.6	B	1.01	0.6
2	62	M	Y	86	94	1.4	88	3.4	1.4	0.8	A	0.91	0.62
3	59	M	N	88	83	0.7	30	3.4	1.2	0.8	B	0.98	0.68
4	47	M	Y	86	80	0.9	46	3.2	1.1	0.8	B	0.93	0.63
5	45	M	N	68	83	1.5	28	3.6	1.2	0.9	A	0.98	0.62
6	45	M	N	88	90	0.9	25	3.8	1.2	1.0	A	0.93	0.65
7	42	M	Y	88	83	5.1	124	3.5	1.5	0.9	B	0.82	0.63
8	45	M	Y	86	90	0.9	22	4.2	1.5	1.1	A	0.82	0.60
9	50	M	Y	88	90	3.0	50	3.2	1.3	0.9	B	0.89	0.62
10	48	M	Y	80	93	0.8	22	3.4	1.3	0.9	B	0.85	0.58
11	50	M	Y	90	95	0.9	21	3.5	1.4	0.8	A	0.88	0.51
12	56	M	Y	78	79	0.9	32	3.8	1.3	0.7	A	0.87	0.63
13	45	M	Y	86	90	0.9	42	3.3	1.2	1.0	B	0.84	0.60
14	50	M	Y	88	84	0.9	36	3.5	1.2	0.9	B	0.86	0.61
15	40	M	Y	86	82	1.1	35	3.6	1.2	0.9	A	0.86	0.62

MASTER CHART
CIRRHOSIS WITH HEPATIC ENCEPHALOPATHY

S no	age	sex	grade	HR	MBP	BIL	AST	alb	PT	Cr	Child	PI	RI
1	45	M	2	74	92	0.8	22	4.2	1.39	2.2	A	0.99	0.64
2	45	M	2	88	80	5.0	47	2.9	1.3	1.4	C	0.88	0.64
3	40	M	1	88	80	1.2	38	3.2	1.33	1.1	B	0.88	0.62
4	40	M	2	100	73	17.4	71	2.4	2.21	1.3	C	1.33	0.78
5	60	M	3	92	83	0.8	22	3.2	1.34	1.3	B	0.92	0.62
6	55	M	2	80	84	8.9	80	3.3	1.8	0.7	C	0.98	0.68
7	47	M	2	88	80	7.2	132	3.1	1.4	1.0	C	0.98	0.62
8	45	M	2	78	76	0.9	46	3.2	1.4	0.8	B	1.01	0.69
9	47	M	3	88	80	5.3	98	2.8	1.9	1.3	C	0.99	0.64
10	48	M	2	86	90	1.1	36	3.1	1.2	0.7	B	1.03	0.68
11	58	M	2	80	86	0.9	46	3.2	1.1	0.8	B	1.03	0.69
12	46	M	1	86	84	0.9	26	3.8	1.2	1.0	B	1.05	0.64
13	52	M	2	86	82	2.6	50	3.2	1.3	0.9	B	1.06	0.64
14	42	M	2	88	80	2.6	56	3.1	1.2	0.9	B	1.01	0.65
15	52	M	2	88	90	1.2	56	3.4	1.3	0.8	B	0.99	0.63